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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/258,600	02/26/1999	Dana M. Fowlkes	CPI-012CP4DV	4086
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Peter C. Lauro, Esq. Lahive & Cockfield, LLP 28 State Street Boston, MA 02109			EXAMINER LAMBERTSON, DAVID A	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/258,600

Applicant(s)

FOWLKES ET AL.

Examiner

David A. Lambertson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2003 and 11 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43-109 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration:
- 5) ☒ Claim(s) 100, 101 and 109 is/are allowed.
- 6) ☒ Claim(s) 43, 46, 48-52, 54-66, 69-93, 96, 97 and 102 is/are rejected.
- 7) ☒ Claim(s) 44, 45, 47, 53, 67, 68, 94, 95, 98, 99 and 103-108 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 May 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Actions, filed May 15, 2003 and November 11, 2003. Amendments were made to the claims. Specifically, new claims 100-109 were added.

Claims 43-109 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed February 12, 2003, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Information Disclosure Statement

The information disclosure statement filed June 19, 2003 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action. Applicant is directed to the crossing out of reference numbers A7, A12, B17, G6 and G10; these references have already been considered on a PTO-892 form, and are thus removed as being duplicate citations. Applicant is notified that references I1 and I2 have been considered in so far as their content; however, Applicant's references I1 and I2 have also been crossed through because the Office will not print Application numbers as references on the patent, should this application go to issue.

Claim Objections

Claims 103-108 are objected to because of the following informalities: claims 103-108 are identical in scope to claims 67, 68, 94, 98 and 99. Claims 103-108 merely recite the limitations of claims 67, 68, 94, 98 and 99 in "long form" (i.e., instead of indicating an independent claim which recites the limitations, the claims write out the limitations that are present in the independent claims). For example, Claim 67 depends from claim 43, and inherently recites the limitations set forth in claim 43; claim 103 simply eliminates the reference to claim 43, instead reciting the limitations of claim 43 within the context of claim 67. Thus, the claims are of identical scope. The same analysis can be made of each of claims 103-108. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43, 48, 54, 57, 58, 60, 61, 63-65, 96, 97 and 102 remain rejected under 35

U.S.C. 102(b) as being anticipated by King et al. (henceforth, King; see entire document) as indicated in the previous Office Action. **This rejection is maintained for the reasons set forth in the previous Office Action, and is now applied to newly added claim 102.**

Response to Arguments Concerning Claim Rejections - 35 USC § 102

Applicant's arguments filed May 15, 2003 have been fully considered but they are not persuasive. Applicant's arguments consist of the following points:

1. The salient feature of the claimed invention is the co-expression of a pheromone system surrogate and a heterologous peptide that *modulates* (original emphasis), i.e., functionally interacts with the pheromone system protein surrogate to generate an intracellular signal. Applicant apparently means "upregulates or downregulates" in terms of modulates, since these terms frequently follow the use of the term "modulates" (see for example page 11 of Applicant's arguments).
2. Applicant suggests that King does not teach a modulator of the pheromone response pathway because: (a) the G α protein functionally couples the pheromone receptor to the pheromone pathway, and therefore *mediates* but does not *modulate* the pheromone system; (b) that without mediation between the receptor and pathway, there can be no modulation; and (c) G α neither "upregulates" nor "downregulates" the pheromone system (see for example, page 11, the second full paragraph and the paragraph bridging pages 11 and 12 of Applicant's arguments).
3. Applicant argues that King does not teach an "autocrine" system as claimed by the instant invention.

Applicant's arguments are not convincing for the following reasons:

- 1 and 2. Applicant's primary point appears to be the distinction between the terms "mediation" and "modulation," where "modulation" is equivalent to the upregulation (agonizing) or downregulation (antagonizing) of the pheromone system. Applicant asserts that King does not

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teach “modulation” as it is understood in the art because $G\alpha$ does not upregulate or downregulate the activity of the pheromone pathway.

Applicant’s argument is not persuasive because $G\alpha$ does indeed modulate the activity of the pheromone pathway. It is well established in the art that the $G\alpha$ subunit acts as a negative regulator of the pheromone cascade (see IDS reference F14; see entire document, in particular the Abstract, last sentence). Since $G\alpha$ is a negative regulator of the signal cascade, it necessarily downregulates or antagonizes the activity of the pheromone pathway; therefore, $G\alpha$ is a modulator as per Applicant’s definition because it can antagonize the pheromone pathway.

Applicant attempts to delineate mediation and modulation as separate phenomena, stating that without mediation there can be no modulation. In the instant case, if $G\alpha$ is to be defined as a mediator, it must also necessarily be defined as a modulator; it is simply that there are no intermediate degrees of modulation, only an “all or nothing” response. It is improper to dismiss $G\alpha$ as a modulator simply because it does not have varying degrees of modulation, only an “all or nothing” modulation. This is because something that antagonizes a response qualifies as a modulator, by Applicant’s own definition set forth in their arguments. In the instant case, $G\alpha$ antagonizes the pheromone response, which is regulated by its interaction with a pheromone receptor; thus, $G\alpha$ meets the functional limitations of a protein that interacts with a pheromone receptor and modulates the activity of a pheromone cascade. In King, both the pheromone receptor (βAR) and the $G\alpha$ protein are heterologous, therefore meeting the limitations of the instant claims.

3. Applicant’s assertion that the claimed invention teaches an “autocrine” system that is not taught by King is a moot point with regard to the instant rejection. The instantly rejected claims

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have no limitation concerning an “autocrine” system. It is further noted that claims that do recite a functionally similar limitation were not rejected in the instant case (e.g., claim 49, where the heterologous peptide is secreted; i.e., an autocrine hormone). Therefore, Applicant is arguing the presence of a limitation that is not present in the instantly rejected claims, which is improper.

In conclusion, Applicant’s assessment of the perceived difference of “mediation” and “modulation” is insufficient to overcome the instant rejection under 35 USC § 102(b). This is because the function of $G\alpha$, as a negative regulator (or antagonist/downregulator) defines it as a modulator as per Applicant’s own arguments. Furthermore, the argument that the King reference does not teach an autocrine system is irrelevant to the instantly rejected claims because this limitation is not present within the claims. Thus the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over King in view of Reneke as set forth in the previous Office Action. **This rejection is maintained for the reasons set forth in the previous Office Action.**

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Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over King in view of Chang as set forth in the previous Office Action. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over King in view of Sikorski as set forth in the previous Office Action. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Response to Arguments Concerning Claim Rejections - 35 USC § 103

Applicant's arguments filed May 15, 2003 have been fully considered but they are not persuasive. Applicant's arguments consist of the following points, which are applicable to each of the rejections collectively (i.e., the arguments are the same for each combination of references):

1. The King reference does not teach each and every limitation of the independent claims (as established in Applicant's arguments regarding the rejections under 35 USC § 102(b)), and this is not remedied by the secondary references (Reneke, Chang or Sikorski) in any of the rejections. Therefore, applicant asserts the combined teachings do not teach the entirety of the claimed invention.
2. That neither the teachings of the primary (King) or the secondary references (Reneke, Chang or Sikorski) teaches all of the elements of the claims on an individual basis. Specifically, Applicant asserts that Reneke, Chang and Sikorski each fail to teach a heterologous surrogate pheromone receptor and a second heterologous peptide on their own.

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3. The Office is using improper hindsight reconstruction to establish a *prima facie* case of obviousness using Applicant's own disclosure. Applicant asserts that the skilled artisan would not have either the motivation to combine the teachings of King with Reneke, Chang or Sikorski, or any expectation of success when practicing the combined references.

Applicant's arguments are not convincing for the following reasons:

1. The Office has adequately established that the King reference does indeed teach a heterologous pheromone receptor, as well as a second heterologous peptide that is capable of modulating the interaction of the heterologous receptor with the pheromone pathway in a cell. Arguments to this effect are presented above in response to the traversal of the rejections under 35 USC § 102(b). Furthermore, the elements that are not taught by the King reference (i.e., mutation of *SST2* or *FAR1*, or the use of the *HIS3* marker gene) are provided for by the secondary references. Thus, Applicant's assertion that the combination of references fails to teach each and every element of the claim is not persuasive.
2. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant is reminded that the combined teachings of the references must be considered when establishing non-obviousness. In the instant case, the secondary references do not need to teach the use of a heterologous pheromone receptor and a second heterologous protein that modulates the interaction between

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the receptor and the pheromone pathway. This is because King establishes these teachings, and it is the combination of the references that establishes the obviousness of the claimed invention.

3. In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The motivation to combine for each rejection will be addressed individually below:

(a) The combination of Reneke and King- Applicant asserts that one of ordinary skill in the art would have no motivation to combine these references because King does not suggest combining the references. However, the Office adequately establishes in the previous Office Action that the teachings of Reneke show the desirability of mutating *SST2* in order to achieve a greater ability to detect activation of a pheromone pathway, and that the King reference involves the detection of activation of a pheromone pathway. Thus one of ordinary skill in the art would be motivated to combine the teachings in order to obtain a greater ability to detect the activation of a pheromone pathway in the assay as taught by King. These teachings are well within the level of ordinary skill at the time the claimed invention was made, and the motivation to combine them is present in the desirability of greater detection of pheromone activation, taught by Reneke. Furthermore, Applicant has provided no reason as to why this motivation is improper, other than their opinion that the Office recreated the invention using the instant specification as a

blueprint. It is noted that Applicant's invention is not the establishment that *SST2* is involved in the pheromone pathway, or that its deletion results in a more sensitive assay for detecting the activity of the pheromone pathway; thus the motivation to combine the references cannot come from using the instant specification as a blueprint, as suggest by Applicant.

(b) The combination of Chang and King- Applicant asserts that one of ordinary skill in the art would have no motivation to combine these references because King does not suggest combining the references. However, the Office adequately establishes in the previous Office Action that the teachings of Chang show the desirability of mutating *FAR1* in order to allow activation of the pheromone response pathway without cell cycle arrest, and that King teaches an assay where measuring the activation of the pheromone pathway is necessary without causing cell cycle arrest (where the cells would not produce a measurable signal). Thus, one of ordinary skill in the art would be motivated to combine the teachings because of the desirability of having an assay where cell cycle arrest would not occur as a result of activation of the pheromone pathway in the assay as taught by King. Furthermore, Applicant has provided no reason as to why this motivation is improper, other than their opinion that the Office recreated the invention using the instant specification as a blueprint. It is noted that Applicant's invention is not the establishment that *FAR1* is involved in the pheromone pathway, or that its deletion results in a more sensitive assay for detecting the activity of the pheromone pathway; thus the motivation to combine the references cannot come from using the instant specification as a blueprint, as suggest by Applicant.

(c) The combination of Sikorski and King- Applicant asserts that one of ordinary skill in the art would have no motivation to combine these references because King does not suggest

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combining the references. However, the Office adequately establishes in the previous Office Action that the teachings of Sikorski show the benefits of using a nutritional selection for screening yeast cells, and that King uses an assay that screens for yeast cells. Thus, one of ordinary skill in the art would be motivated to combine the screening techniques of King and Sikorski because of the benefits of using a nutritional selection, which is established by the teachings of Sikorski. Applicant's assertion that the use of an enzymatic assay versus a nutritional selection represents a teaching away is unclear, as there is nothing in either the King or the Sikorski references to suggest that the use of an enzymatic assay necessarily excludes the use of a nutritional selection assay (in fact, many of the nutritional selection markers involve the enzymatic production of amino acid precursors, and are effectively "enzymatic assays" at the most rudimentary level). Furthermore, Applicant has provided no reason as to why this motivation is improper, other than their opinion that the Office recreated the invention using the instant specification as a blueprint. It is noted that Applicant's invention is not the establishment that *HIS3* is a nutritional marker that can be used in a selection process; thus the motivation to combine the references cannot come from using the instant specification as a blueprint, as suggest by Applicant.

In conclusion, the rejections of claims 55, 56 and 59 are maintained because Applicant has not provided a persuasive argument as to why the claimed invention is not obvious over the indicated references. The Office has established that the combined teachings indeed teach all of the claimed limitations, and has provided adequate motivation, as taught by the references themselves, for combining the references. Furthermore, Applicant has not provided any

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evidence as to why such motivation would be improper, aside from a blanket assertion that the Office has recreated the invention from Applicant's own invention. As a result, the rejections under 35 USC 103(a) are maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 43, 46, 48-52, 54-66 and 69-93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-18, 24, 29, 35, 36, 38, 39 and 41 of U.S. Patent No. 6,100,042. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Because Applicant has not provided substantial arguments to the incorrectness of the rejection, no such arguments can be addressed, and the rejection is maintained.

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Allowable Subject Matter

Claims 100, 101 and 109 are allowed.

Claims 103-108 are objected to as being duplicate claims.

Claims 44, 45, 47, 53, 67, 68, 94, 95, 98 and 99 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636



JAMES KETTER
PRIMARY EXAMINER